OIPE IAP69
JUL 12 2006
PATENT & TRADEMARK OFFICE

TRANSMITTAL FORM

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Application Number	09/903,954
Filing Date	July 12, 2001
First Named Inventor	GARST
Group Art Unit	1618
Examiner Name	Fay, Z.
Total Number of Pages in This Submission	24
Attorney Docket Number	A05009CIPCON

ENCLOSURES *(check all that apply)*

- [X] Fee Transmittal Form *(in duplicate)*
- [X] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) ____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [X] Appeal Communication to TC *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [X] Other Enclosure(s) *(please identify below)*

Two cited references

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Stout, Uxa, Buyan & Mullins, LLP		
Signature			
Printed Name	Carlos A. Fisher		
Date	7/10/06	Reg. No.	36,510

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OIPE IAP69 JUL 12 2006 PATENT & TRADEMARK OFFICE

FEE TRANSMITTAL for FY 2005

Patent fees are subject to annual revision.

☐ Application claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 500

Complete if Known	
Application Number	09/903,954
Filing Date	July 12, 2001
First Named Inventor	GARST
Examiner Name	Fay, Z.
Art Unit	1618
Attorney Docket No.	A05009CIPCON

METHOD OF PAYMENT *(check all that apply)*

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☒ Deposit Account Deposit Account Number 01-0885 Deposit Account Name Carlos A. Fisher

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fees Paid ($)**
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

Subtotal (1) 0

2. EXCESS CLAIM FEES

Fee Description	**Fee ($)**	**Small Entity Fee ($)**
Each claim over 20 or , for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple Dependent Claims	360	180

Total Claims ____ -20 or HP = ____ x **Fee ($)** ____ **Fee Paid ($)** ____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims ____ -3 or HP = ____ x **Fee ($)** ____ **Fee Paid ($)** ____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims — **Fee ($)** ____ **Fee Paid ($)** ____

Subtotal (2) 0

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets ____ -100 = **Extra Sheets** ____ /50= **Number of each additional 50 or fraction thereof** ____(round **up** to a whole number) x **Fee ($)** ____ = **Fee Paid ($)** ____

Subtotal (3) 0

4. OTHER FEE(S) **Fee Paid ($)**

- ☐ Surcharge - Late filing fee or oath/declaration: $130 fee ($65 small entity discount)
- ☐ Non-English Specification: $130 fee (no small entity discount)
- ☐ 1-month extension of time: $120 fee ($60 small entity discount)
- ☐ 2-month extension of time: $450 fee ($225 small entity discount)
- ☐ 3-month extension of time: $1020 fee ($510 small entity discount)
- ☐ 4-month extension of time: $1590 fee ($795 small entity discount)
- ☐ 5-month extension of time: $2160 fee ($1080 small entity discount)
- ☐ Information Disclosure Statement Fee: $180 fee (no small entity discount)
- ☐ Notice of Appeal: $500 fee ($250 small entity discount)
- ☒ Filing a Brief in Support of Appeal: $500 fee ($250 small entity discount) — 500
- ☐ Request for Oral Hearing: $1000 fee ($500 small entity discount)
- ☐ Utility Issue Fee: $1400 fee ($700 small entity discount)
- ☐ Recording each patent assignment per property (times number of properties): $40 fee (no small entity fee discount)
- ☐ Request for Continued Examination: $790 fee ($395 small entity discount)
- ☐ Other: ____

Subtotal (4) 500

SUBMITTED BY

Name (Print/Type)	Carlos A. Fisher	*Registration No. (Attorney/Agent)*	36,510	*Telephone*	949-450-1750
Signature	Carlos A Fisher			*Date*	7/10/06

OIPE IAP69 JUL 12 2006 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Garst
Serial No.: 09/903,954
Conf. No.: 3028
Filed: July 12, 2001
For: COMBINATIONS OF PROSTAGLANDINS AND BRIMONIDINE OR DERIVATIVES
Group Art Unit: 1614
Examiner: Fay, Z.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, Alexandria, VA 22313-1450 on:

Date of Deposit: July 10, 2006
Person making Deposit: Alicia Curran
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Date of Signature: 7/10/06

Commissioner for Patents
Alexandria, VA 22313-1450

APPEAL BRIEF

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TABLE OF CONTENTS

REAL PARTY IN INTEREST

The sole inventor, Michael E. Garst, assigned his entire interest in this patent application to Allergan Sales, Inc. via an assignment document recorded at reel 011717, frame 0317 and executed on November 15, 1999. Allergan Sales, Inc. was subsequently merged with Allergan Sales, L.L.C. Allergan Sales, L.L.C. then assigned its entire interest in this application to Allergan, Inc.

Allergan, Inc., is therefore the owner of this patent application and the real party in interest in this appeal.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS

Claims 1 – 20 and 26 have been cancelled without prejudice.

Claims 21-25 and 27 are pending, have been rejected, and are under appeal.

STATUS OF AMENDMENTS

An amendment of claims 21 and 24 pursuant to 37 CFR §41.33 was filed on July 7, 2006 after the filing of a Notice of Appeal. These amendments were made solely in order to simplify the claims and place them in better condition for consideration on appeal. Applicants have not yet received confirmation that this amendment was entered in the present application.

No other amendments have been made since the mailing date of the Final Office Action on November 2, 2005.

The Claims Appendix of this Appeal Brief lists the claims as they appeared prior to the 37 CFR §41.33 Amendment filed July 7, 2006.

SUMMARY OF CLAIMED SUBJECT MATTER

The present application contains a single independent claim, claim 21.

Claim 21 is drawn to a method of treating degeneration of the optic nerve of a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a prostaglandin and a therapeutic amount of an alpha adrenergic receptor agonist of a given structure. Support for this claim can be found on e.g., page 5, lines 25-32 and pages 8 and 9 of the specification. The words "and retinal ganglion cells" were deleted from the preamble of this claim in a Rule 41.33 Amendment filed July 7, 2006; while the Claims Appendix lists the claims as they stand before entry of this Amendment, Applicants have argued the patentability of the claims on the basis of the entry of this Amendment.

Claim 22 is a dependent claim in which the prostaglandin is selected from a Markush group of specific compounds. Beyond the listed support for claim 21, support for this Markush group is found, e.g., on pages 12 and 13 of the specification.

Claim 23 is a dependent claim in which the prostaglandin is selected from a Markush group of specific compounds. Beyond the listed support for claim 21, support for this Markush group is found, e.g., on pages 12 and 13 of the specification.

Claim 25 depends from claim 14 in which the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine). Beyond the listed support for claim 21, support for this amendment can be found e.g., on page 13, lines 6-20. Because claim 14 is a cancelled claim, Applicants changed the dependency of this claim by replacing "14" with "23" in a Rule 41.33 Amendment filed July 7, 2006. While the Claims Appendix lists the claims as they stand before entry of this Amendment, Applicants have argued the patentability of the claims on the basis of this Amendment.

Claim 27 depends from claim 21 in which the prostaglandin is the 11-pivalyl ester of PGF2α and the alpha adrenergic agent is brimonidine. Beyond the listed support for claim 21, support for this amendment is found in originally filed claim 13.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 21-25 and 27, all the currently pending claims, have been rejected as allegedly *prima facie* obvious over Yavitz, E., OCULAR SURG. NEWS 17:28 (September 1999) and Woodward (US Patent 5,877,211).

ARGUMENT

I. CLAIM 21

a. Did the Examiner err in holding that Claim 21 is *prima facie* obvious over the combination of Yavitz, E., OCULAR SURG. NEWS 17:28 (September 1999) (hereinafter "*Yavitz*") and Woodward (U.S. Patent 5,877,211) (hereinafter "*Woodward*")?

i. ***The Examiner has not met the burden of establishing a prima facie conclusion of obviousness, because nothing in the combination of the Yavitz and Woodward references motivates or suggests to one of ordinary skill in the art to combine an alpha adrenergic agonist and a prostaglandin for the currently claimed purpose for the treatment of degeneration of the optic nerve.***

Claim 21 has been amended in a Rule 41.33 Amendment to delete the words "and the retinal ganglion cells" from method claim 21. While the Claims Appendix shows claim 21 in its unamended state, Applicants have argued the patentability of this and dependent claims as a method for the treatment of degeneration of the optic nerve.

In order to establish a proper conclusion of *prima facie* obviousness, the burden is on the patent examiner to establish that the cited references 1) suggest or provide motivation to the person of ordinary skill in the art to combine reference teachings, 2) provide a reasonable expectation of success to such as person in making the claimed invention, and 3) teach or suggest all the claim limitations, either alone or when combined. See e.g., MANUAL OF PATENT EXAMINING PROCEDURE §2142 at 2100-134 (8th Ed., Rev. 4, 2006) (hereinafter "MPEP"); see also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). The Applicants respectfully submit that the Examiner has not met this burden in the present case.

The invention of Claim 21 is drawn to a method for the treatment of degeneration of the optic nerve by administration to a mammal in need thereof of an alpha adrenergic agonist of a given generic structure and a prostaglandin.

Yavitz describes the results of a small study (20 patients) in which thinning of the retinal nerve fiber layer was seen in almost all patients undergoing laser in situ keratomileusis (LASIK). The hypothesis set forth in the reference is that nerve damage is due either to hypoxia (oxygen starvation) or apoptosis due to a crush injury, possibly a

mechanical injury caused by elevated intraocular pressure (IOP), transiently required during LASIK. See *Yavitz* at 28, col. 1, ¶ 3. These effects were reported to be mitigated or prevented by administration of brimonidine for one week preop and for 4 weeks postop. The author concludes that the data implies that brimonidine may be neuroprotective. *Id.* at col. 3, ¶ 4.

Woodward discusses the ability of certain agonists of the prostaglandin EP2 receptor to protect cultured rat hippocampal neurons in cell culture against challenge with the excitatory amino acids glutamate, α-amino-3-hydroxy-5-methyl-4-isoxazole proPionic acid (AMPA), N-methyl-D-aspartate (NMDA), or kainic acid. Interestingly, Woodward states "[i]t is noted that PGF2α and PGF2α 1-OH are inactive [in this assay], thereby indicating that this [protective result] is a specific EP2 receptor mediated effect." U.S. Patent No. 5,877,211 (the '211 patent), column 8, lines 49-51 (emphasis added). Woodward notes that this effect is independent of the ability of an EP2 receptor agonist to lower IOP, since PGF2α is said to be a potent hypotensive despite its inactivity in the neuroprotection experiments described in the Examples of the Woodward patent. *See id.* at paragraph bridging columns 2 and 3 and column 8, lines 49-51.

There is no teaching or suggestion in the combination of these references that would motivate a person of ordinary skill in the art to combine an alpha adrenergic agonist and a prostaglandin in the treatment of degeneration of the optic nerve. Although Woodward discusses the use of EP2 agonists to treat ocular nerve damage, not all such agonist compounds are themselves prostaglandins. Yavitz does not discuss agents other than brimonidine and Woodward does not discuss alpha adrenergic agonists.

Moreover, Woodward teaches away from the use of "prostaglandins" generally as neuroprotectants, since prostaglandin PGF2α and other prostaglandin FP2α receptor agonists are said to be "inactive". The term "neuroprotection" in Woodward, as evidenced by e.g., claim 1 of the '211 patent, appears to be construed to exclude any neuroprotective benefits attendant to lowering IOP (and thus avoiding a mechanical crushing injury to retinal neurons). That the person of ordinary skill in the art would so adopt this interpretation is a reasonable assumption from a reading the text of Woodward, since prostaglandin F2α, a potent ocular hypotensive, is said not to be active. '211 patent, column 8, lines 49-51.

Yavitz notes that the use of a single alpha adrenergic agonist, brimonidine, prior to and following LASIK surgery lessens the thinning of the retinal nerve fiber layer observed in the absence of such brimonidine use. The Yavitz study is not described in detail, and the reference points out that the LASIK-related nerve loss may be due to a "crushing injury" caused by raising the IOP to 80 mm Hg or greater. Yavitz at column 1,

¶ 3. Brimonidine is shown to mitigate this injury. However, Yavitz does not mention optic nerve degeneration or teach or even suggest the use of brimonidine to treat such injury. Indeed, the only conditions mentioned by Yavitz are retractive surgery, such as LASIK, and glaucoma. Yavitz does not disclose whether other IOP-lowering agents were used as controls to test the hypothesis that brimonidine is neuroprotective. Finally, Yavitz does not mention or even suggest the use of prostaglandins.

Each and every limitation of a claim must be either suggested or taught by the prior art in order to establish a *prima facie* case of obviousness. See e.g., MPEP § 2143.03, citing *In re Wilson*, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970). Neither Yavitz nor Woodward, alone or in combination teaches or suggests a method for treating degeneration of the optic nerve, treating any condition with a combination of a prostaglandin and an alpha agonist, or teaches or suggests the generic alpha agonist structure presented in claim 21.

Applicants thus believe it is manifest that neither Yavitz nor Woodward, alone or in combination with the other, teaches, suggests, or motivates one of ordinary skill in the art to conceive of the present invention, comprising a method for the treatment of degeneration of the optic nerve comprising administering an alpha adrenergic agonist and a prostaglandin to a patient in need thereof, with a reasonable expectation of success.

For these reasons, the Applicants respectfully request that the Board of Patent Appeals and Interferences *reverse* the Examiner's holding that claim 21 is *prima facie* obvious over the combination of Yavitz and Woodward.

II. CLAIM 22

a. Did the Examiner err in holding that Claim 22 is *prima facie* obvious over the combination of Yavitz, E., OCULAR SURG. NEWS 17:28 (September 1999) and Woodward (U.S. Patent 5,877,211) ?

i. ***The Examiner has not met the burden of establishing a prima facie conclusion of obviousness, because nothing in the combination of the Yavitz and Woodward references motivates or suggests to one of ordinary skill in the art to combine an alpha adrenergic agonist of the specified generic structure and a prostaglandin selected from the Markush group of prostaglandins contained in claim 22 for the currently claimed purpose for the treatment of degeneration of the optic nerve.***

Claim 22 is dependent from claim 21, described above. In this claim the prostaglandin is selected from a Markush group that includes a variety of prostaglandins.

Applicants respectfully believe this claim is not *prima facie* obvious for the reasons set forth in reference to claim 21, above, and hereby incorporate the arguments herein by reference.

In addition, neither Yavitz nor Woodward, alone or in combination with the other, teaches, suggests, or motivates one of ordinary skill in the art to select a compound set forth in the Markush group of claim 22 in combination with an alpha-adrenergic component for the treatment of degeneration of the optic nerve.

Yavitz is silent with regard to conditions other than refractive surgery and glaucoma, and with regard to any compounds other than brimonidine. Woodward is drawn only to EP2 agonists as neuroprotective agents. However, Woodward does not teach, suggest or indeed provide any reason or motivation for one to combine an EP2 agonist with an alpha-adrenergic agonist.

ii. *The Examiner has not met the burden of establishing a prima facie conclusion of obviousness, because Woodward teaches away from the claimed invention.*

Woodward states that prostaglandin F2α and its derivatives are "inactive", and that neuroprotection is a "specific EP2 receptor mediated effect". '211 patent, column 8, lines 49-51. Indeed, Woodward is really only concerned with, and only provides data concerning the EP2 agonists PGE2 and trans-2-[-4(1-hydroxyhexyl)phenyl]-5-oxocyclopentaneheptanoicacid; see '211 patent, paragraph bridging columns 4 and 5 and Figures 1C and 1D. Thus, Woodward teaches away from the use of prostaglandins *per se*, and from prostaglandins other than prostaglandin EP2, such as prostaglandin F2α and its derivatives, which are all part of this Markush group. Thus, Woodward teaches away from the invention of claim 22.

III. CLAIM 23

a. Did the Examiner err in holding that Claim 23 is *prima facie* obvious over the combination of Yavitz, E., OCULAR SURG. NEWS 17:28 (September 1999) and Woodward (U.S. Patent 5,877,211)?

i. ***The Examiner has not met the burden of establishing a prima facie conclusion of obviousness, because nothing in the combination of the Yavitz and Woodward references motivates or suggests to one of ordinary skill in the art to combine an alpha adrenergic agonist of the specified generic structure and a prostaglandin selected from the Markush group of prostaglandins contained in claim 23 for the currently claimed purpose for the treatment of degeneration of the optic nerve.***

Claim 23 is dependent from claim 22, described above. In this claim the prostaglandin is selected from a Markush group that includes a variety of prostaglandin F2α derivatives.

Applicants respectfully believe this claim is not obvious for the reasons set forth in reference to claims 21 and 22, above, and hereby incorporate the arguments made with respect to these claims herein by reference.

In addition, neither Yavitz nor Woodward, alone or in combination with the other, teaches, suggests, or motivates one of ordinary skill in the art to select a compound comprising a prostaglandin F2α or derivatives thereof to combine with an alpha adrenergic agonist (including brimonidine) in the treatment of degeneration of the optic nerve. Indeed, the Examiner has not alleged that the prior art does accomplish this.

ii. ***The Examiner has not met the burden of establishing a prima facie conclusion of obviousness, because Woodward teaches away from the use of compounds other than prostaglandin EP2 receptor agonists as neuroprotectants.***

Woodward states that prostaglandin F2α and its derivatives are "inactive", and that neuroprotection is a "specific EP2 receptor mediated effect". '211 patent, column 8, lines 49-51. Indeed, Woodward is really only concerned with, and only provides data concerning the EP2 agonists PGE2 and trans-2-[-4(1-hydroxyhexyl)phenyl]-5-oxocyclopentaneheptanoicacid; see '211 patent, paragraph bridging columns 4 and 5 and Figures 1C and 1D. Thus, Woodward teaches away from the use of prostaglandins *per se*, and from prostaglandins other than prostaglandin EP2, such as prostaglandin F2α and its derivatives, the only members of the "prostaglandin" Markush group of claim 23. Thus, Woodward teaches away from the invention of claim 23.

CLAIM 24

b. Did the Examiner err in holding that Claim 24 is *prima facie* obvious over the combination of Yavitz, E., OCULAR SURG. NEWS 17:28 (September 1999) and Woodward (U.S. Patent 5,877,211)?

i. ***The Examiner has not met the burden of establishing a prima facie conclusion of obviousness, because nothing in the combination of the Yavitz and Woodward references motivates or suggests to one of ordinary skill in the art to combine an alpha adrenergic agonist of the specified generic structure contained in claim 24 with a prostaglandin for the currently claimed purpose for the treatment of degeneration of the optic nerve.***

Claim 24 is dependent from claim 21, described above. In this claim the alpha adrenergic agonist is selected from compounds meeting the criteria set forth in the generic structure of the Markush group of claim 24.

Applicants respectfully believe this claim is not obvious for the reasons set forth in reference to claim 21 above, and hereby incorporate the arguments made with respect to these claims herein by reference.

In addition, neither Yavitz nor Woodward, alone or in combination with the other, teaches, suggests, or motivates one of ordinary skill in the art to select a compound comprising a prostaglandin F2α or derivatives thereof to combine with brimonidine or any other alpha adrenergic agonist in the treatment of degeneration of the optic nerve. This is only the more evident given the narrower generic claim setting forth the species of alpha adrenergic compounds encompassed in the method of claim 24.

As stated above, each and every limitation of a claim must be either suggested or taught by the prior art in order to establish a *prima facie* case of obviousness. See e.g., MPEP § 2143.03, citing *In re Wilson*, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970). Neither Yavitz nor Woodward, alone or in combination teaches or suggests a method for treating degeneration of the optic nerve, treating any condition with a combination of a prostaglandin and an alpha agonist, or teaches or suggests the generic alpha agonist structure present in claim 24.

IV. CLAIM 25

a. Did the Examiner err in holding that Claim 25 is *prima facie* obvious over the combination of Yavitz, E., OCULAR SURG. NEWS 17:28 (September 1999) (hereinafter "*Yavitz*") and Woodward (U.S. Patent 5,877,211) (hereinafter "*Woodward*")?

i. ***The Examiner has not met the burden of establishing a prima facie conclusion of obviousness, because nothing in the combination of the Yavitz and Woodward references motivates or suggests to one of ordinary skill in the art to combine brimonidine with a prostaglandin of the structure required by claim 25 for the currently claimed purpose for the treatment of degeneration of the optic nerve.***

Claim 25 is dependent from claim 14, a cancelled claim. Applicants have filed a Rule 41.33 Amendment, which has not yet been indicated as entered, in which this error has been corrected to make this claim dependent from claim 23, described above. In this claim the alpha adrenergic agonist is further limited to brimonidine. Applicants argument are directed to the claim with its dependency corrected.

Applicants respectfully believe this claim is not obvious for the reasons set forth in reference to claims 21, 22 and 23 above, and hereby incorporate the arguments made with regarding to these claims herein by reference.

In addition, neither Yavitz nor Woodward, alone or in combination with the other, teaches, suggests, or motivates one of ordinary skill in the art to select a compound set forth in the Markush group of claim 23 in combination with brimonidine for the treatment of degeneration of the optic nerve.

Yavitz is silent with regard to the use of brimonidine for conditions other than refractive surgery and glaucoma. Woodward is drawn only to EP2 agonists as neuroprotective agents. However, Woodward does not teach, suggest or indeed provide any reason or motivation for one to combine an EP2 agonist with an alpha-adrenergic agonist generally or brimonidine in particular. The combination of Yavitz and Woodward does not lead the person of ordinary skill in the art to the method of claim 25, much less provide, as is required by law, any reasonable expectation in doing so.

V. CLAIM 27

a. Did the Examiner err in holding that Claim 27 is *prima facie* obvious over the combination of Yavitz, E., OCULAR SURG. NEWS 17:28 (September 1999) and Woodward (U.S. Patent 5,877,211)?

i. ***The Examiner has not met the burden of establishing a prima facie conclusion of obviousness, because nothing in the combination of the Yavitz and Woodward references motivates or suggests to one of ordinary skill in the art to combine brimonidine with the 11-pivalyl ester of PGF2α for the currently claimed purpose for the treatment of degeneration of the optic nerve.***

Claim 27 is dependent from claim 21, described above. In this claim the alpha adrenergic agonist is further limited to brimonidine and the prostaglandin to the 11-pivalyl ester of PGF2α.

Applicants respectfully believe this claim is not obvious for the reasons set forth in reference to claims 21, 22 and 23 above, and hereby incorporate the arguments made with regard to these claims herein by reference.

In addition, neither Yavitz nor Woodward, alone or in combination with the other, teaches, suggests, or motivates one of ordinary skill in the art to select the 11-pivalyl ester of PGF2α to combine with brimonidine for the treatment of degeneration of the optic nerve.

ii. ***The Examiner has not met the burden of establishing a prima facie conclusion of obviousness, because Woodward teaches away from the use of compounds other than prostaglandin EP2 receptor agonists as neuroprotectants.***

Woodward states that prostaglandin F2α and its derivatives are "inactive", and that neuroprotection is a "specific EP2 receptor mediated effect". '211 patent, column 8, lines 49-51. Indeed, Woodward is really only concerned with, and only provides data concerning the EP2 agonists PGE2 and trans-2-[-4(1-hydroxyhexyl)phenyl]-5-oxocyclopentaneheptanoicacid; see '211 patent, paragraph bridging columns 4 and 5 and Figures 1C and 1D. Thus, Woodward teaches away from the use of prostaglandins *per*

se, and from prostaglandins other than prostaglandin EP2, such as prostaglandin F2α and its derivatives. The sole prostaglandin required by claim 27 is the 11-pivalyl ester of PGF2α. Woodward therefore teaches away from the invention of claim 27.

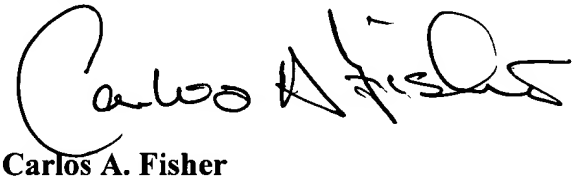
Yavitz provides no teaching whatsoever with regard to the use of prostaglandins or prostaglandin receptor agonists. Thus, Yavitz cannot make up for the deficiency of Woodward.

CONCLUSION

For the foregoing reasons Applicants respectfully request that the Board affirm the patentability of the pending claims, as amended in the Rule 42.33 Amendment filed July 7, 2006, by reversing the Examiner's holding of obviousness. Each of the claims has been argued separately, thus the claims each stand or fall independently of the other claims.

Applicants have filed herewith either a check or deposit account authorization for payment of the fee associated with the filing of this Appeal Brief. If any other fee is due, Applicants hereby authorize the Commissioner to use Deposit Account 01-0885 for the payment of such fee.

Respectfully submitted,



Carlos A. Fisher
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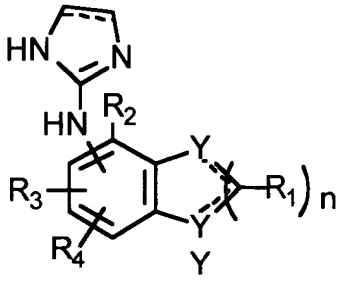
CLAIMS APPENDIX

STATUS OF CLAIMS

(not including Rule 41.33 Amendment)

1-20 (Cancelled)

21) (Previously presented) A method of treating degeneration of the optic nerve and the retinal ganglion cells of a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)



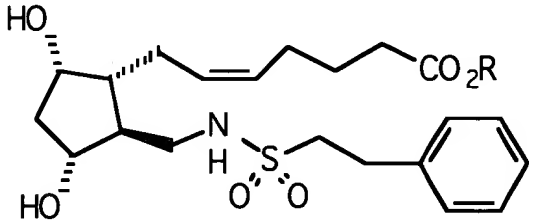
formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH3, O, S and C-R1; R1 is hydrogen, lower alkyl or oxo; R2, R3 and R4 are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates either a single or a double bond, provided that two double bonds are not on the same carbon in the case when n=1, and their pharmaceutically acceptable salts and esters as appropriate.

22. (Original) The method of claim 21 wherein the prostaglandin is selected from the group consisting of PGF2α, PGE2, PGE1, prostacyclin, 15(S)-methyl-PGF2α, 16,16-dimethyl-

PGF2α, 15(S)-methyl-PGE2a, 16,16-dimethyl-PGE2, 17,18,19,20-tetranor-16-phenoxy-PGE2, 17,18, 19,20-tetranor-16-phenoxy-PGF2α, 18,19,20-trinor-17-phenyl-PGE2, 18,19,20-trinor-17-phenyl-PGF2α, the free acid and lower alkyl esters of PGF2α, wherein the omega chain has been replaced with phenylethylsulfonamidomethyl- , trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy PGF2α, sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE2, 11-deoxy-PGF2α, 11-deoxy-16,16-dimethyl-PGE2, 11-deoxy-15(S)-methyl-PGE2, 11-deoxy-15(S)-methyl-PGF2α, misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

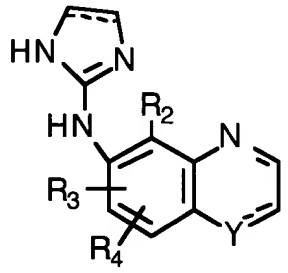
23) (Original) The method of claim 22 wherein the prostaglandin is selected from the group consisting of PGF2α-11-pivalyl ester, the 1-amido-15-methyl ether of PGF2α, 1-ethylamido-18,19,20-trinor-17-phenyl-PGF2α, PGF2α-1-ethyl ester, PGF2α1-isopropyl ester, the acid and isopropyl ester derivatives of PGF2α wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



R=H, i-propyl,

RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-PGF2α-1-methyl ester.

24) (Original) The method of claim 21 wherein the alpha adrenergic agent is selected from the group consisting of formula (II) wherein Y is N or O, R2 is bromine or methyl and all other variables are defined as in claim 14



formula (II)

25) (Original) The method of claim 23 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

26) (Cancelled)

27) (Previously presented) The method of claim 21 wherein the prostaglandin is the 11-pivalyl ester of PGF2α and the alpha adrenergic agent is brimonidine.

EVIDENCE APPENDIX

1. Yavitz, E., OCULAR SURG. NEWS 17:28 (September 1999).
2. Woodward (US Patent 5,877,211).

BEST AVAILABLE COPY

Ocul Surg News 1999 Sep 1;17(17):28.

A

99091344A

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Gram-negative bacteria:
Pseudomonas aeruginosa
Serratia marcescens
Anaerobic species:
Propionibacterium acnes

for this organism was studied in fewer than 10 infections

INDICATIONS

...olution is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in ...ation.

...NGS

...INJECTION.

...olution should not be injected subconjunctivally, nor should it ...luced directly into the anterior chamber of the eye.

...and occasionally fatal hypersensitivity (anaphylactic) reactions, ...llowing the first dose, have been reported in patients receiving ...quinolones, including ofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema ...ng laryngeal, pharyngeal or facial edema), airway obstruction, ...dyspnea, and itching. A rare occurrence of Stevens-Johnson ...e, which progressed to toxic epidermal necrolysis, has been ...d in a patient who was receiving topical ophthalmic ofloxacin. If an ...reaction to ofloxacin occurs, discontinue the drug. Serious acute ...sensitivity reactions may require immediate emergency treatment, ...and airway management, including intubation should be administered ...ppropriately indicated

...TIONS

...al: As with other anti-infectives, prolonged use may result ...rowth of non-susceptible organisms, including fungi. If superinfections discontinue use and institute alternative therapy. Whenever ...judgment dictates, the patient should be examined with the aid of ...ation, such as slit lamp biomicroscopy and, where appropriate, ...n staining. Ofloxacin should be discontinued at the first appearance of a rash or any other sign of hypersensitivity reaction.

...ernic administration of quinolones, including ofloxacin, has led to ...l lesions of the cartilage in weight-bearing joints and other signs ...athy in immature animals of various species. Ofloxacin, administered systemically at 10 mg/kg/day to young dogs (equivalent to 110 times ...imum recommended daily adult ophthalmic dose) has been ...d with these types of effects.

...tion for Patients: Avoid contaminating the applicator tip with ...rom the eye, fingers or other source.

...quinolones, including ofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately, contact your physician at the first sign of a rash or allergic reaction.

...teractions: Specific drug interaction studies have not been ...d with OCUFLOX ophthalmic solution. However, the systemic ...ration of some quinolones has been shown to elevate plasma ...evels of theophylline, interfere with the metabolism of caffeine, and ...the effects of the oral anticoagulant warfarin and its derivatives, and ...associated with transient elevations in serum creatinine in patients ...cyclosporine concomitantly.

...genesis, Mutagenesis, Impairment of Fertility: Long term ...o determine the carcinogenic potential of ofloxacin have not been ...d.

...was not mutagenic in the Ames test, in vitro and in vivo cytogenetic ...ster chromatid exchange assay (Chinese hamster ovary) and human cell ...nscheduled DNA synthesis (UDS) assay using human fibroblasts, ...mant lethal assay, or mouse micronucleus assay. Ofloxacin was ...in the UDS test using rat hepatocyte, and in the mouse lymphoma ...

...studies in rats, ofloxacin did not affect male or female fertility or ...logical or reproductive performance at oral dosing up to 360 ...g (equivalent to 4000 times the maximum recommended daily ...ic dose).

...gy: Teratogenic Effects. Pregnancy Category C: Ofloxacin ...shown to have an embryocidal effect in rats and in rabbits when ...doses of 810 mg/kg/day (equivalent to 9000 times the maximum ...mended daily ophthalmic dose) and 160 mg/kg/day (equivalent to ...s the maximum recommended daily ophthalmic dose). These ...esulted in decreased fetal body weight and increased fetal mortality ...d rabbits, respectively. Minor fetal skeletal variations were reported ...ering doses of 810 mg/kg/day. Ofloxacin has not been shown to be ...at doses as high as 810 mg/kg/day and 160 mg/kg/day when ...red to pregnant rats and rabbits, respectively.

...togenic Effects. Additional studies in rats with doses up to ...g/day during late gestation showed no adverse effect on late fetal ...ent, labor, delivery, lactation, neonatal viability, or growth of the ...

...However, no adequate and well-controlled studies in pregnant ...OCUFLOX solution should be used during pregnancy only if the ...ential justifies the potential risk to the fetus.

Mothers: In nursing women a single 200 mg oral dose resulted in ...tions of ofloxacin in milk which were similar to those found in ...It is not known whether ofloxacin is excreted in human milk ...following ophthalmic administration. Because of the potential for ...verse reactions from ofloxacin in nursing infants, a decision ...should be made whether to discontinue nursing or to discontinue the drug, ...account the importance of the drug to the mother.

...Use: Safety and effectiveness in infants below the age of one ...not been established.

...es, including ofloxacin, have been shown to cause arthropathy ...ure animals after oral administration; however, topical ocular ...ation of ofloxacin to immature animals has not shown any ...y. There is no evidence that the ophthalmic dosage form of ...has any effect on weight bearing joints.

...E REACTIONS

...mic Use: The most frequently reported drug-related adverse ...was transient ocular burning or discomfort. Other reported ...include stinging, redness, itching, chemical ...hosis/erythema, periocular/facial edema, foreign body sensation, ...ia, blurred vision, tearing/dryness, and eye pain. Rare reports of ...have been received.

LASIK study shows brimonidine provides neuroprotective effect

LASIK study has far-flung neuroprotective implications, physician says.

SEATTLE – A small, double-masked study showed almost universal nerve fiber layer thinning after laser in situ keratomileusis (LASIK).

Further, the study showed that the nerve fiber thinning was mitigated or totally prevented by brimonidine (Alphagan; Allergan). **Edward Yavitz, MD,** clinical assistant professor at the University of Illinois College of Medicine, reported his findings at the annual American Society of Cataract and Refractive Surgery meeting.

"... if Alphagan indeed shows neuroprotection, it becomes the premier glaucoma drop, at least until another drop shows the same kind of neuroprotectivity."
— Edward Yavitz, MD

"The hypothesis was that raising the pressure in the eye to 80 mm Hg or above, which all microkeratomes must do in order to make a flap, causes nerve loss in the nerve fiber layer due to either hypoxia or apoptosis of the nerve fiber layer due to a crush injury, and that brimonidine mitigates this nerve loss," Dr. Yavitz told OCULAR SURGERY NEWS. "It's important not to panic anyone into thinking that any harm is being done by LASIK. The nerve fiber layer is normal in thickness before and after surgery; it's just that relatively it has decreased in some patients between 5% and 10%."

A sensitive measurement

Twenty patients were asked to use brimonidine in one eye for 1 week preop and 4 weeks postop LASIK and were randomly assigned a placebo drop in the opposite eye. Bilateral LASIK was performed, limiting the suction time for 40 seconds. Eye pressure during microkeratome usage was checked with a pneumotonograph. Nerve fiber analysis was performed with a GDx Nerve Fiber Analyzer (Laser Diagnostic Technologies; San Diego) before surgery and at 1 month and 3 months after surgery.

"It was simply a matter of finding the most sensitive measure of nerve fiber layer viability that allowed me to demonstrate these very small changes in the nerve fiber layer," Dr. Yavitz said.

into the tracks, it could take 60 seconds of suction time."

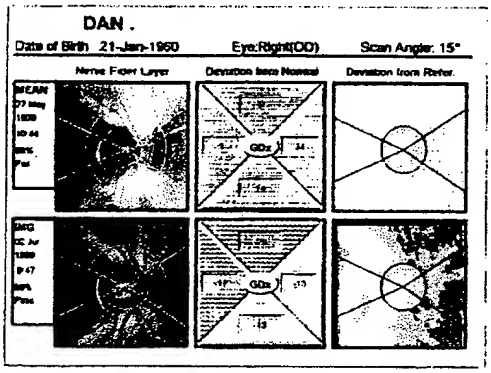
In tests following his pilot study, Dr. Yavitz found that if the suction time was kept under 20 seconds, there was very little nerve fiber change seen. The average suction time for LASIK depends on the skill of the surgeon and how fast the two parts of the microkeratome can be integrated once the suction ring takes hold, according to Dr. Yavitz.

"It appears that the disposable keratomes that have integrated suction and cutter are perhaps a little faster to use and might reduce the time of suction," he said.

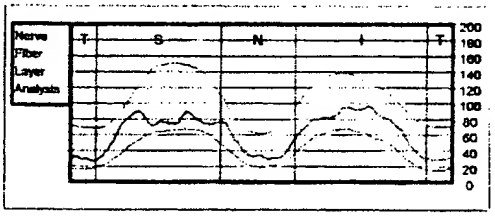
The further implication in his finding, Dr. Yavitz said, is that for one of the first times, it has been demonstrated on a limited basis that brimonidine is neuroprotective.

"Neuroprotectivity is a hot topic, and it has never been proven in a human before. It has been shown in rat eye studies, but never in human eyes. So the major implication of this is not in refractive surgery at all, but in the fact that if Alphagan indeed shows neuroprotection, it becomes the premier glaucoma drop, at least until another drop shows the same kind of neuroprotectivity," Dr. Yavitz told OCULAR SURGERY NEWS.

by Rochelle Nataloni
Correspondent



A 39-year-old male with −3.5 D who underwent LASIK. Preoperative and 1-month postoperative GDx analysis is shown. Areas of nerve fiber loss are colored blue.



The graphic analysis of the postoperative GDx shows that the nerve fiber layer is 40 µm thinner in the superior and inferior arcade. The overall nerve fiber thickness, however, is within normal limits (shaded area).

Larger study and implications

"This was a small study, so we need to repeat it with much larger numbers," Dr. Yavitz said. He said that Allergan is funding a follow-up study comprising 1,000 patients at four sites around the country. "Our goal with the larger study is to demonstrate that [the pilot study findings] are real. That would then suggest that patients undergoing LASIK might be given brimonidine for 3 days before the surgery and 1 week after the surgery as a prophylactic measure to protect the axons in the nerve fiber layer against apoptosis," Dr. Yavitz said.

The larger study will allow surgeons with different keratomes and different lasers to participate.

"It also will allow us to see if this [result] is time dependent. We're not going to restrict participants to 40 seconds of suction time; we'll let them do it at their own pace," Dr. Yavitz said. "Sometimes when you get the keratome caught on the lid or it doesn't [easily] fit

For Your Information:

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■**Allergan** can be reached at 2525 Dupont Drive, Irvine, CA 92612; (714) 246-4500; fax: (714) 246-4162.

■**Laser Diagnostic Technologies** can be reached at 9550 Waples St., Ste. 105, San Diego, CA 92121; (800) 722-6393 or (858) 558-9144; fax: (858) 558-9145; Web site: www.laserdiagnostic.com.

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